REMARKS

Claim Amendments

Claims 43, 44, 48, 59-64, and 66 are canceled without prejudice.

Claims 40 and 65 are amended and new Claims 67-88 are added. Support for these claims is found in the specification as filed. For example, support for the amendments to Claims 40, 65, and new Claims 77, 82, 87 and 88 is in the specification at page 19, lines 8-14, page 26, line 12 through page 27, line 16; page 29, line 15 through page 30, line 3; page 19, lines 8-14; page 17, lines 4-9; page 39, lines 17-21 and page 40, lines 9-12. Claims 67, 68, 72, 73 and 88 are supported at page 39, lines 17-21; and at page 40, lines 9-12. Claims 69, 74, 79, and 84 are supported at page 41, lines 1-2. Claims 70, 75, 80, and 85 are supported at page 45, lines 9-10. Claims 78, 83 and 87 are supported at page 19, lines 8-14. Claims 71, 76, 81 and 86 are supported at page 36, Table1.

Rejection of Claims 40, 48, 65 and 66 Under 35 U.S.C. § 112, First Paragraph

Claims 40, 48, 65 and 66 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, a pore size range of 200-780 μm is rejected as representing new matter.

Applicants have amended the claims. As presented, the claims do not recite a pore size range of 200-780 μm. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 40, 43, 59, 60, 65 and 66 Under 35 U.S.C. § 102(a)

Claims 40, 43, 59, 60, 65 and 66 are rejected under 35 U.S.C. § 102(a) as being anticipated by Hutmacher *et al.* ("Design and Fabrication of a 3D Scaffold for Tissue Engineering Bone" as published in Agrawal *et al.*, Eds. *Synthetic Bioabsorbable Polymers for Implants*. ASTM, West Conshohocken, PA (2000) pp. 152-167).

Applicants are filing concurrently herewith a Declaration Under 37 C.F.R. § 1.132 by the inventors of the present application which evidences the Hutmacher *et al.* reference describes Applicants' own work. The Declaration Under 37 C.F.R. § 1.132 is signed by all inventors except Iwan Zein, who is unavailable. Iwan Zein is unavailable to join in this Declaration because his current address is unknown. Diligent effort has been made to contact Iwan Zein by

mailing the Declaration to his last known address. Mail delivery failed because the addressee was not found at the last known address. A copy of the mailing label and return receipt indicating delivery failure is attached as Exhibit A.

As evidenced by the Declaration Under 37 C.F.R. § 1.132, the Hutmacher *et al.* reference describes Applicants' own work. Applicants' disclosure of their own work within the year before the application filing date cannot be used against the Applicants under 35 U.S.C. § 102(a) (see *In re Katz*, 687 F. 2d 450, 215 U.S.P.Q. 14 (CCPA 1982)). Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 40, 43, 44, 48, 50, 51 and 56-66 Under 35 U.S.C. § 103(a)

Claims 40, 43, 44, 48, 50, 51 and 56-66 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Richter *et al.* (U.S. Patent No. 6,280,478), Cima *et al.* (U.S. Patent No. 5,518,680) and Jang *et al.* (U.S. Patent No. 6,129,872), as evidenced by Kuslich (U.S. Patent No. 5,549,679).

Applicants' Claimed Invention

The claims as currently pending, are directed to, *inter alia*, an apparatus for use in tissue engineering. In one embodiment, the scaffold is made by layering and adhering sequential layers of scaffold material that is polycaprolactone (PCL) or a polycaprolactone/ceramic composite, such as polycaprolactone/hydroxyapatite (PCL/HA) or polycaprolactone/tricalcium phosphate (PCL/TCP) (see Claims 40, 65, 81 and 86, and claims dependent thereon). In another embodiment, the scaffold is made by layering and adhering sequential layers of scaffold material at raster angles of 0°/60°/120° to produce a triangular pattern of scaffold material when viewed in the z-axis, or laid at raster angles of 0°/72°/144°/36°/108° to produce a polygonal pattern of scaffold material when viewed in the z-axis (see Claims 67, 68, 75, 76, 80, and 85, and claims dependent thereon). The ratio of the raster road width to the channel width is constant in each layer. The resulting scaffold apparatus is highly porous with interconnecting pores with large internal surface areas that make the scaffold apparatus particularly suitable for tissue engineering applications (see, *e.g.*, specification page 41, lines 6-9). The scaffold designs of Applicants are such that they allow the flow transport of nutrients and waste (specification page 41, lines 9-11), they have the capacity to deliver a high volume of cells (specification page 41, lines 11-12), they

have the chemical and physical properties that allow load-bearing applications, as well as allowing active tissue integration of bone and cartilage tissue components and vascularization to enhance nutrient transport (specification page 41, lines 12-16). The "interconnected and highly regular honeycomb-like pore morphology" of Applicants' scaffolds "supports the development of a vascular network, which is able to regulate the transport of nutrients and waste in the entire scaffold architecture" (specification page 46, lines 10-17). The features and applications of Applicants' scaffolds in tissue engineering is further evidenced in the Examples, see particularly Example 2, subsection (vi), titled "Results" (specification page 59, line 14 through page 63, line 4).

Background

As discussed in the application as filed, many different processing techniques have been developed to design and fabricate three-dimensional (3D) scaffolds for tissue engineered implants (specification page 12, line 2, *et seq.*). As explained in the specification, these conventional techniques include fiber bonding, solvent casting, particulate leaching, membrane lamination, melt molding, temperature-induced phase separation (TIPS), and gas foaming. A wide range of scaffold characteristics, such as porosity and pore size, have been reported using such fabrication techniques. However, there are ***numerous drawbacks*** to using such scaffolds for tissue engineering applications. For example, the pores are ***not fully interconnected*** due to the formation of skin-layers during solvent evaporation. The ***pore size varies***, as it is difficult to ensure that the porogens are well-dispersed and not agglomerated to form bigger particles. In addition, the thickness and length of the pore walls and edges vary, depending on the solvent evaporation rate. Also, the scaffolds ***cannot*** be made with thick sections inasmuch as deeply embedded porogens become too distant from the surface and residual porogens may be left in the final structure. Also, the use of organic solvents requires careful and complete removal of residual solvents prior to clinical usage.

As discussed in Hutmacher *et al.* in "Mechanical properties and cell cultural response of polycaprolactone scaffolds designed and fabricated via fused deposition modeling" published in *J. Biomed. Mat. Res.* (2001) 55 (2): 203-216 (submitted as Exhibit 2 with the Amendment filed January 9, 2009 and cited above), no single technique has allowed researchers to design and fabricate scaffolds with a completely interconnected pore network, a highly regular and

reproducible scaffold morphology, and is solvent-free (Hutmacher *et al.*, page 204, left column). Hutmacher *et al.*, goes on to explain that "These are essential scaffold features to facilitate cell proliferation and differentiation, extracellular matrix synthesis, and flow transport of nutrients and wastes. *In vivo*, the scaffold structure should protect the inside of the pore network proliferating cells and their extracellular matrix from being mechanically overloaded for a sufficient period of time. This is especially critical for load-bearing tissues such as bone and cartilage" (Hutmacher *et al.*, page 204, left column).

Applicants have taught and described in the application as filed a scaffold with a completely interconnected pore network, a highly regular and reproducible scaffold morphology, and which is solvent-free. Applicants' scaffold designs have several advantages over conventional scaffolds. For example, Applicants' scaffold designs allow the flow transport of nutrients and waste (specification page 41, lines 9-11), have the capacity to deliver a high volume of cells (specification page 41, lines 11-12), have the chemical and physical properties that allow load-bearing applications, as well as allowing active tissue integration of bone and cartilage tissue components and vascularization to enhance nutrient transport (specification page 41, lines 12-16). The "interconnected and highly regular honeycomb-like pore morphology" of Applicants' scaffolds "supports the development of a vascular network, which is able to regulate the transport of nutrients and waste in the entire scaffold architecture" (specification page 46, lines 10-17).

References Cited in Support of Obviousness Rejection

The references Richter *et al.* (U.S. Patent No. 6,280,478), Cima *et al.* (U.S. Patent No. 5,518,680) and Jang. (U.S. Patent No. 6,129,872), as evidenced by Kuslich (U.S. Patent No. 5,549,679) are cited by the Examiner to support the assertion that Applicants' claimed invention is obvious.

Applicants respectfully disagree. It would not have been obvious for a person of skill in the art to combine the cited references to arrive at the claimed invention not least because there were so many divergent techniques available and conventionally used by others to make scaffold structures (*e.g.*, fiber bonding, solvent casting, particulate leaching, membrane lamination, melt molding, temperature-induced phase separation (TIPS), and gas foaming). Furthermore, fused deposition modeling (FDM) was "[u]sually . . . used to fabricate ***solid*** models" (specification

page 18, lines 2-3; emphasis added). In contrast, the scaffold structures as claimed are not solid, but instead are highly ***porous***.

Still further, the specific materials used in the claimed scaffolds and specific raster angles of the sequential layers would not be obvious to one of skill in the art. There are many different materials used to make implants scaffolds, *e.g.,* as described in Cima *et al.*, "A number of materials are commonly used to form a matrix….including polymers and monomers which can be polymerized or adhered to form an integral unit" (Cima *et al.*, column 6-7, bridging sentence). Cima *et al.* further describes several examples of suitable polymers:

> such as a synthetic thermoplastic polymer, for example, ethylene vinyl acetate, poly(anhydrides), polyorthoesters, polymers of lactic acid and glycolic acid and other α hydroxy acids, and polyphosphazenes, a protein polymer, for example, albumin or collagen, or a polysaccharide containing sugar units such as lactose. The polymer can be non-biodegradable or biodegradable, typically via hydrolysis or enzymatic cleavage. Non-polymeric materials can also be used to form the matrix…. Examples include organic and inorganic materials such as hydoxyapatite, calcium carbonate, buffering agents, and lactose, as well as other common excipients used in drugs, which are solidified by application of adhesive rather than solvent.
>
> Photopolymerizable, biocompatible water-soluble polymers include polyethylene glycol tetraacrylate (Ms 18,500) which can be photopolymerized with an argon laser under biologically compatible conditions using an initiator such as triethanolamine, N-vinylpyrrolidone, and eosin Y. Similar photopolymerizable macromers having a poly(ethylene glycol) central block, extended with hydrolyzable oligomers such as oligo(d,l-lactic acid) or oligo(glycolic acid) and terminated with acrylate groups, may be used.
>
> Examples of biocompatible polymers with low melting temperatures include polyethyleneglycol 400 which melts at 4°-8°C. PEG 600 which melts at 20°-25°C., and PEG 1500 which melts at 44°-48°C. another low melting material is stearic acid, which melts at 70°C.
>
> Other suitable polymers can be obtained by reference to The Polymer Handbook, 3rd edition (Wiley, N.Y., 1989). Cima *et al.* column 7, lines 5-39.

Cima *et al.* goes on to describe that:

> A preferred material is a polyester in the polylactide/polyglycolide family. These polymers have received a great deal of attention in the drug delivery and tissue regeneration areas for a number of reasons. They have been in use for over 20 years in surgical sutures, are Food and Drug Administration (FDA)-approved and have a long and favorable clinical record. A wide range of physical properties and degradation times can be achieved by varying the monomer ratios in lactide/glycolide copolymers: poly-L-lactic acid (PLLA) and poly-glycolic acid (PGA) exhibit a high degree of crystallinity and degrade relatively slowly, while copolymers of PLLA and PGA, PLGAs, are amorphous and rapidly degraded. Although attempts have been made to develop true surface-eroding polymer, for example, polyanhydrides, the relationship between polymer composition and device properties are very difficult to control in practice by standard fabrication techniques. Cima *et al.* column 7, lines 41-57.

Furthermore, even if combined, a person of skill in the art would not arrive at Applicants' claimed invention from the cited references since the combination of the references fails to teach or suggest Applicants' claimed invention. The teachings of each of the cited references are further discussed in turn below.

Richter *et al.* (U.S. Patent No. 6,280,478)

Richter *et al.* is generally directed to a three-dimensional lattice structure for use as a bone implant where bone growth is required (Richter *et al.* Abstract). More specifically, Richter *et al.* discloses a method for making a lattice structure whereby an organic binder base or material is prepared to which hydroxylapatite ceramic powder is mixed, heated and extruded in a three-dimensional layered lattice (Richter *et al.*, column 3, lines 39-58). The layered lattice (referred to as a "green artefact" [sic]), is then "heated to remove the organic material, by slow heating it in a furnace from room temperature to 600°C. at a rate not exceeding 40°/hour. ***Thereafter, the lattice structure is sintered at 1250°C. for 3 hours to form the artefact*** [sic] ***in which the bars or laths of the lattice components are fused together in the zones where they cross***" (see Richter *et al.*, column 4, lines 22-27; emphasis added).

There is no teaching or suggestion in Richter *et al.* to make a scaffold structure "by depositing sequential layers of scaffold material under conditions sufficient to adhere each

sequential layer to the adjacent layer" as claimed by Applicants. Indeed, if the Richter *et al.* method was applied to polycaprolactone (PCL), the lattice structure would simply breakdown because PCL has a glass transition temperature of -60°C, a melting point (T_m) of 60°C and a decomposition temperature of 350°C (specification, page 18, lines 13-20).

In the Office Action, it is asserted that "the variations in pattern lay-down, including variations in shape from round, to triangular, or five-sided, are known variations of the prior art and they would have been predictable to one of skill in the art at the time the invention was made. The motivation to choose particular angles comes from the '478 patent, which teaches that components can extend at any angle between 10 degrees and 90 degrees relative to those of an adjacent component" (Office Action, page 6).

Applicants respectfully disagree with this assertion. Richter *et al.* discloses that "the laths of one lattice component can extend at any angle between 10° and 90° relative to those of an adjacent component" (Richter *et al.*, column 3, lines 21-23). However, but this is only an invitation to experiment. As evidenced by Applicants' specification as filed, and as published in Hutmacher *et al.* (cited above), scaffolds with different raster angles exhibited ***significantly different*** compressive stiffness and offset yield strength under ambient conditions in air and under simulated physiological conditions (see specification page 53-54 and Hutmacher *et al.,* page 208 through page 209, under heading "Compression testing".). Thus, it would ***not be predictable*** which combination of raster angles would have desirable properties for a scaffold structure. Consequently, merely disclosing that "the laths of one lattice component can extend at any angle between 10° and 90° relative to those of an adjacent component" (Richter *et al.*, column 3, lines 21-23) is merely an invitation to experiment. It would not be predictable to a person of skill in the art whether any specific angle between 10° and 90° will exhibit desired properties for a scaffold structure. That the angles for different shapes are known does not support how to predict which combination of raster angles will be suitable for a scaffold structure for use in tissue engineering. Thus, without a specific teaching or suggestion of the specific angles as claimed by Applicants, a person of skill in the art would not immediately arrive at Applicants' claimed invention from Richter *et al.*

Cima *et al.* (U.S. Patent No. 5,518,680)

Cima *et al.* generally describes solid free-form techniques for making medical devices for implantation and growth of cells, including stereo-lithography (SLA), selective laser sintering (SLS), ballistic particle manufacturing (BAM), fusion deposition modeling (FDM), and three dimensional painting (3DP) (*e.g.*, Cima *et al.* Abstract). More particularly, Cima *et al.* describes making composite devices using 3DP (see, *e.g.,* Cima *et al.*, column 9, lines 34-53; column 10, lines 63-67; column 11, lines 1-45; column 11, line 46 through column 12, line 25; column 12, lines 43-51; column 13, line 36 through column 14, line 18; and Examples 1 and 2). Cima *et al.* does not teach or suggest an apparatus for use in tissue engineering as claimed.

In contrast to the assertion that Cima *et al.* demonstrates that the "composition (i.e. PLC and PLC/HA) of the claimed scaffold is old and well-known in the art" (Office Action, page 7), Cima *et al.* does not teach or suggest that the matrix material can be polycaprolactone (PCL) or a polycaprolactone/ceramic composite, such as polycaprolactone/hydroxyapatite (PCL/HA) or polycaprolactone/tricalcium phosphate (PCL/TCP). Cima *et al.* teaches that its matrices are made from polymers and "[d]epending on the processing method, the polymer forming the matrix may be in solution, as in the case of SLA, or in particle form, as in the case of SLS, BPM, FDM, and 3DP" (Cima *et al.*, column 6, lines 39-42). Exemplary polymers taught by Cima *et al.* include synthetic thermoplastic polymers "ethylene vinyl acetate, poly(anhydrides), poly-orthoesters, polymers of lactic acid and glycolic acid and other α hydroxy acids, and polyphosphazenes, a protein polymer, for example, albumin or collagen, or a polysaccharide containing sugar units such as lactose" (Cima *et al.,* column 7, lines 6-10).

At most, Cima *et al.* describes that "[s]olvents and/or binder are used in the preferred method, 3DP, as well as SLA and BPM. The binder can be a solvent for the polymer and/or bioactive agent or an adhesive which binds the polymer particles" (Cima *et al.,* column 7, lines 60-64). Cima *et al.* describes that such a binder (*i.e.*, a ***solvent*** for the polymer and/or bioactive agent or an ***adhesive***) "can be a resorbable polymer such as polylactic acid or polycaprolactone of molecular weight 50,000-200,000, in a solvent such as chloroform or a mixture of chloroform and a less-volatile solvent such as ethyl acetate to minimize warping" (Cima *et al.,* column 8, lines 36-40). Thus, Cima *et al.* does not teach or suggest that the matrix material can be polycaprolactone (PCL) or a polycaprolactone/ceramic composite, such as

polycaprolactone/hydroxyapatite (PCL/HA) or polycaprolactone/tricalcium phosphate (PCL/TCP).

Furthermore, Cima *et al.* does not teach or suggest that the ratio of the raster road width to the channel width is constant in each layer. At most, Cima *et al.* teach layers with varying raster road width to the channel width, specifically detailed as "1st layer: Lines 100 microns wide spaced 300 microns center-to-center along the length of the 2 cm axis (each line is 200 microns in depth), for a total of 30 lines. Triplets of 100 micron wide lines (*i.e.*, three lines printed side by side) with 100 micron spacing in between printed along the 1-cm axis, for a total of 25 triplets, to decrease the number of channels accessible from the outside. 2nd layer: Lines 100 microns wide spaced 300 microns center-to-center along the length of the 2-cm axis; these lines are 200 microns in depth and placed directly above the lines in the previous layer. The spaces between the lines will form the longitudinal channels. 3rd layer: Lines 100 microns wide with 100 microns spacing in between …." (Cima *et al.,* column 14, lines 28-44, et seq.; emphasis added). Such a matrix does not have a constant ratio of the raster road width to the channel width in each layer as claimed in Applicants' invention.

Still further, Cima *et al.* does not teach or suggest a scaffold structure wherein the scaffold is made by layering and adhering sequential layers of scaffold material at raster angles of 0°/60°/120° to produce a triangular pattern of scaffold material when viewed in the z-axis, or laid at raster angles of 0°/72°/144°/36°/108° to produce a polygonal pattern of scaffold material when viewed in the z-axis. As discussed above, Cima *et al.* describe specific layering of the matrix such that the lines alternate along the 2 cm axis and 1 cm axis of a rectangular device of 2 cm x 1 cm x 1 cm dimensions (see Cima *et al.* Example 1 at column 14). As will be apparent to those of ordinary skill in the art, the resulting matrix will have a 0°/90°/180°/270° pattern.

It is asserted in the office action that "the '680 patent teaches that it would be desirable to control pore size, shape and tortuosity, including connectedness, during the shaping operation" (Office Action, page 6). However, it is respectfully pointed out that the full context of this quote is in the discussion of ***desired*** properties for tissue regeneration devices and that the recited factors "are ***difficult to control*** using standard processing techniques" (Cima *et al.*, column 2, lines 1-2; emphasis added). Such statements demonstrate what a person of skill in the art may

wish to achieve, but by no means demonstrates the obviousness of the specific properties of the scaffold structure as claimed by Applicants.

To summarize, Cima *et al.* does not teach or suggest an apparatus for use in tissue engineering wherein the scaffold is made by layering and adhering sequential layers of scaffold material that is polycaprolactone (PCL) or a polycaprolactone/ceramic composite, such as polycaprolactone/hydroxyapatite (PCL/HA) or polycaprolactone/tricalcium phosphate (PCL/TCP), or wherein the scaffold is made by layering and adhering sequential layers of scaffold material at raster angles of $0^{o}/60^{o}/120^{o}$ to produce a triangular pattern of scaffold material when viewed in the z-axis, or laid at raster angles of $0^{o}/72^{o}/144^{o}/36^{o}/108^{o}$ to produce a polygonal pattern of scaffold material when viewed in the z-axis, and wherein the ratio of the raster road width to the channel width is constant in each layer.

Jang (U.S. Patent No. 6,129,872)

It is asserted in the Office Action that Jang teaches how one of skill in the art can arrive at the materially relevant limitations of the instant claims (Office Action, page 5).

Applicants respectfully disagree. Jang generally teaches making ***solid*** objects. More specifically, Jang is directed to an apparatus and process for producing a multi-color object from a computer-aided design image of the object by incorporating a multi-channel colorant-injecting module into a device, such as a system used in FDM (see, *e.g.*, Jang, column 3, lines 44-56; and column 4, lines 8-16). Jang does not teach or suggest a scaffold material having interconnected channels. Furthermore, Jang does not teach or suggest that each layer of the scaffold structure is formed by depositing raster roads of melt extrusion filament material, wherein a fill gap between each raster road provides a horizontal channel, and wherein the ratio of the raster road width to the channel width is constant in each layer. Furthermore, Jang does not teach or suggest a scaffold material that is formed in layers of melt extrusion filament material selected from polycaprolactone (PCL), a polycaprolactone/hydroxyapatite (PCL/HA) composite, or a polycaprolactone/tricalcium phosphate (PCL/TCP) composite, or wherein the raster angles of the melt extrusion filament material are $0^{o}/60^{o}/120^{o}$ or $0^{o}/72^{o}/144^{o}/36^{o}/108^{o}$ in the z-axis view.

Thus, in contrast to the assertion in the Office Action, Jang does not teach or suggest the materially relevant limitations of the present claims.

Kuslich (U.S. Patent No. 5,549,679)

Kuslich is cited to evidence that the bioceramic hydroxyapatite is bioresorbable (Office Action, page 5).

Kuslich is generally directed to a fabric bag packed with graft medium for inserting into the spine (see, *e.g.* Kuslich Abstract). Kuslich discloses that the "fill opening may be a bushing that could be bioabsorbable such as hydroxyapatite or it could be plastic or metal" (Kuslich column 7, lines 47-50).

However, Kuslich fails to remedy the defects of Richter *et al.*, Cima *et al.* and Jang. In particular, Kuslich does not teach or suggest an apparatus for use in tissue engineering wherein the scaffold is made by layering and adhering sequential layers of scaffold material that is polycaprolactone (PCL) or a polycaprolactone/ceramic composite, such as polycaprolactone/hydroxyapatite (PCL/HA) or polycaprolactone/tricalcium phosphate (PCL/TCP), or wherein the scaffold is made by layering and adhering sequential layers of scaffold material at raster angles of $0^{\circ}/60^{\circ}/120^{\circ}$ to produce a triangular pattern of scaffold material when viewed in the z-axis, or laid at raster angles of $0^{\circ}/72^{\circ}/144^{\circ}/36^{\circ}/108^{\circ}$ to produce a polygonal pattern of scaffold material when viewed in the z-axis, and wherein the ratio of the raster road width to the channel width is constant in each layer.

Thus, the combination of Richter *et al.*, Cima *et al.*, and Jang in view of Kuslich, does not teach or suggest Applicants' claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Request for Telephonic Interview

Applicants' representative respectfully requests a telephonic interview to expedite prosecution.

Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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